

## CASE REPORT

# Transfusion associated graft versus host disease in an immunocompetent individual following coronary artery bypass grafting

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## Abstract

**Transfusion associated graft versus host disease (TA-GVHD) is a rare but commonly fatal complication of transfusion of cellular blood products, which usually occurs in immunosuppressed individuals following transfusion and subsequent engraftment of viable T lymphocytes. Very rarely it may arise in apparently immunocompetent individuals. A case is reported of TA-GVHD in a non-immunocompromised 60 year old white man, resulting from red cell transfusion after coronary artery bypass grafting. HLA typing confirmed homozygosity of the donor for an HLA type shared by the recipient—the classic scenario for the development of TA-GVHD in immunocompetent individuals. The patient died 21 days after transfusion. There is a perceived increased risk of TA-GVHD following bypass grafting and other surgical procedures where cardiopulmonary bypass is required. TA-GVHD is probably underreported and the incidence in the UK is felt to be too low to warrant routine irradiation of cellular products for this group of patients. Clinicians, pathologists, and transfusion centres should be aware of this rare but devastating complication of blood transfusion after cardiac surgery.**

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A 60 year old white man with unstable angina and angiographic evidence of double vessel disease was admitted for elective coronary artery bypass grafting (CABG). His preoperative blood count and biochemical parameters including renal function and liver function were normal. Surgery was relatively uncomplicated but six days postoperatively his haemoglobin was 79 g/l and he was transfused with two units of red cell concentrate, which were less than 72 hours old.

Fourteen days after transfusion he was readmitted with a history of diarrhoea, fever, and rash. Over the following 72 hours he developed profound, progressive pancytopenia and acute

hepatitis, the fever and diarrhoea persisted, and the skin rash worsened. A bone marrow aspirate and trephine biopsy revealed aplastic marrow. A skin biopsy from an affected area showed basal cell vacuolation, single cell death, a lymphocytic inflammatory cell infiltrate, and focal basal liquefaction. These appearances, given the clinical history, are highly suggestive of graft versus host disease (GVHD). Despite full supportive care with blood products and broad spectrum antibiotics he continued to have swinging pyrexia, worsening hepatitis, and bone marrow failure; he died 21 days after transfusion. Postmortem examination showed features consistent with GVHD in the skin, liver, small bowel, kidney, and bone marrow.

## HLA typing

To investigate further the development of transfusion associated (TA) GVHD, blood samples from the implicated donors, and blood and tissue samples from the recipient were HLA typed. HLA class I serological typing was performed using a modified microlymphocytic technique,<sup>1</sup> and HLA class II polymerase chain reaction sequence specific primers typing was performed using a set of 24 primer mixes (supplied by Dynal Ltd, Bromborough, UK).<sup>2</sup> The recipient tissue type was HLA A1,B8,DR3(17),DR 6(13) with no evidence of chimerism detected. One of the donors was homozygous for HLA A1, B8, and DR3, and therefore shared five of six major HLA antigens with the recipient, producing the optimal scenario for the development of TA-GVHD in an immunocompetent individual.

## Discussion

TA-GVHD arises four to 30 days after transfusion as a result of engraftment in the recipient of viable transfused lymphocytes from cellular blood products. It is typically seen in individuals with profound defects of cell mediated immunity, but on rare occasions it is seen in apparently immunocompetent individuals. Diagnosis may be confirmed histologically by skin biopsy, and HLA typing and other molecular methods can be used to demonstrate donor lymphocyte engraftment. Death follows the development of TA-GVHD in more than 90% of cases<sup>3</sup> and there is no therapeutic agent of

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proved value. Irradiation of cellular blood products to 25 Gy can effectively prevent the development of this condition,<sup>4</sup> currently available blood filters are not deemed a suitable alternative.

TA-GVHD in immunocompetent individuals appears most commonly following CABG and other cardiovascular surgery in which cardiopulmonary bypass is required.<sup>5</sup> The reasons for this are not entirely clear but it is thought, that the use of relatively fresh blood with more viable lymphocytes increases the chance of engraftment. In a review of TA-GVHD after cardiac surgery in Japan, on 71% of occasions the implicated transfused red cells were less than 72 hours old.<sup>3</sup> Whether the potential risk of TA-GVHD associated with using fresh cellular products is justifiable is open to debate. Although it is clear that lymphocyte viability is affected by storage, the benefits of using fresh products after cardiopulmonary bypass are less well documented. Some studies have shown a reduction in blood loss after cardiopulmonary bypass in recipients of fresh blood compared to stored blood,<sup>6</sup> but there is a paucity of evidence for an overall clinical benefit or for reduction in homologous blood transfused. In addition, cardiopulmonary bypass appears to produce a transient state of immunodeficiency defined by reduced mitogenic lymphocyte transformation and reduced interleukin 2 production.<sup>7</sup>

TA-GVHD in immunocompetent individuals occurs more commonly when a blood donor is homozygous for one of the recipients major HLA types. It is suggested that because of the shared haplotype the host fails to recognise donor cells as foreign thus allowing engraftment. The viable T lymphocytes from the donor then mount a fulminant immune response against the host producing the clinical picture described above. Clearly, the risk of TA-GVHD in immunocompetent hosts increases in areas of low genetic diversity where the chance of shared HLA haplotypes with blood donors is increased.

The reported frequency of one way matching or sharing HLA haplotype in a non-first degree relative in Japan ranges from 1 in 312<sup>8</sup> to 1 in 874,<sup>5</sup> and as a result more than 200 cases of TA-GVHD have been reported in immuno-

competent individuals in Japan. Greater HLA diversity probably accounts for the greatly reduced incidence of TA-GVHD in immunocompetent white patients.

Guidelines on the indications for irradiation of cellular blood products to prevent the development of TA-GVHD, which have recently been published, do not recommend the routine irradiation of blood products for patients undergoing cardiopulmonary bypass.<sup>4</sup> However, these guidelines and other transfusion practices will be kept under review with careful reference to the recently introduced serious hazards of transfusion (SHOT) initiative.<sup>9</sup> For this reason cases of TA-GVHD and other serious complications of blood transfusion should be reported to SHOT by haematologists responsible for hospital blood banks.

The use of cellular blood products during cardiac surgery has fallen over recent years owing to improved surgical techniques, preoperative haemodilution, the use of aprotinin, and red cell salvage techniques. In addition, the safety of blood transfusion has improved as a result of developments in compatibility testing and detection of viral infection. Despite these improvements, the potential for other rare but devastating complications of transfusion such as TA-GVHD persists.

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